REMARKS

Claims 1 – 25, 27, and 37 – 39 are pending in the application. Claims 1 and 16 have been amended. Claims 4 and 5 have been cancelled. No new claims have been added. No new matter has been added by virtue of the amendments, support being found throughout the specification and from the pending claims. Applicants further note that claim 26 is also "canceled" herein. The application, as filed, omitted claim 26.

Claim Rejections- 35 U.S.C. § 103(a)

Claims 1 – 7, 9, 12 – 22, 24, 37 - 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Judd et al (U.S. Patent No. 5,910,112; the '112 reference) in view of Berg et al. (U.S. Patent No. 5,128,121; the '121 reference). Applicants respectfully traverse the rejection.

^{21}Na MRI detects myocardial infarction through altered sodium levels associated with cardiac tissue impaired sodium-potassium pump function of non-viable tissue after acute infarction and reperfusion. Thus, ^{23}Na MRI signal elevations are associated with non-viable myocardium. In addition to infarcted cardiac tissue, ^{23}Na MRI produces an intense signal for ventricular blood present in ventricular cavities. As a result, there are minimal signal intensity differences between the signal for infarcted cardiac tissue and the ventricular cavities. This lack of signal intensity differences hampers the detection of infracted myocardium tissue. ^{39}K MRI suffers from similar problems. The instant invention solves this problem.

The instant claims provide methods for evaluating myocardial tissue using ^{23}Na or ^{39}K magnetic resonance imaging (MRI), comprising treating the myocardial tissue with an iron oxide contrast agent so as to attenuate the ^{23}Na or ^{39}K MRI signal for ventricular cavity blood and viable well-perfused tissue, and then imaging the tissue with ^{23}Na or ^{39}K magnetic resonance to detect infracted myocardial tissue and provide contrast between the ventricular cavity and infarcted myocardial tissue, thus evaluating the myocardial tissue. As taught in the specification, the heart presents unique considerations in regard to assessing cardiac tissue:

> in the heart, the problem of low spatial resolution of ^{23}Na MRI images is further compromised by the high sodium content of ventricular blood which hinders differentiation of the ventricular wall from the ventricular cavity, and hence the differentiation of elevated sodium in myocardial infarction (MI). Thus, there tends to be minimal contrast between the ventricular cavity and infarcted cardiac tissue (page 2, lines 5 – 10).

The '112 reference does not relate to a method or composition for performing ^{23}Na and ^{39}K MRI on cardiac tissue so as to address the problem of minimal signal intensity differences between the signal for infarcted cardiac tissue and ventricular blood present in the ventricular cavities. The '112 reference relates to ^{23}Na and ^{39}K magnetic resonance imaging of the heart and the use of such imaging to assess cardiac cell viability. The '112 reference provides:

> a process of identifying regional areas of myocardial damage in vivo. The process includes the step of imaging the heart in vivo using ^{23}Na or ^{39}K magnetic resonance imaging wherein regions of relative high image ^{23}Na intensity and regions of relative low ^{39}K intensity indicate the damages regions. The damaged regions of the myocardium are non-viable tissue resulting from any pathological condition such as ischemia. ^{23}Na and ^{39}K images are obtains using fast gradient echo imaging techniques optimized to maximize signal acquisition by exploiting the short T1 of ^{23}Na and ^{39}K thereby reducing imaging times to a few minutes (col 14, lines 3 – 14).

The '112 reference teaches manipulation and optimization of imaging parameters so as to increase the overall magnetic resonance (MR) signals for ^{23}Na and ^{39}K to a detectable level. The '112 reference teaches optimization of imaging parameters, such as by increasing voxel size, lengthening imaging time taking, employing fast imaging pulse sequences, using GRE imaging, and varying the selection of receiver bandwidth(see e.g. col. 6, lines 10-11, 19-21, 57-59, and 66-67) such that "the combination of approaches disclosed (will) result in an increase in signal sufficient to achieve the requirements for clinical sodium imaging (col 16, lines 29 – 32)."

The '112 reference does not relate to a method or composition for performing ^{23}Na and ^{39}K MRI on cardiac tissue so as to address the problem of minimal signal intensity differences

between the signal for infarcted cardiac tissue and ventricular blood present in the ventricular cavities. As set forth in the specification and described above, imaging the heart presents unique problems of low spatial resolution which hinders differentiation between ventricular cavity and infarcted tissue. The '112 reference simply teaches a process of identifying regional areas of myocardial damage in vivo, and neither teaches nor suggests use of the method to detect infracted myocardial tissue and provide contrast between the ventricular cavity and infarcted tissue. In fact, the '112 reference does not even suggest that the presence of ventricular blood in the ventricular cavities can cause a problem with ^{23}Na or ^{39}K MRI imaging of infracted myocardium tissues, or how and if this problem can be solved. The '112 reference states that:

> to be clinically useful, it is necessary to acquire sodium images of the heart with voxel dimensions a few millimeters on each side and imaging times of a few minutes. Superficially, these requirements would appear very difficult to meet in light of the fact that the sodium MR signals is approximately 10,000 times smaller than that of protons. The result of the studies disclosed herein show that the combination of approaches disclosed herein results in an increase in signal sufficient to achieve the requirements for clinical sodium imaging (col 16, lines 29 – 32).

The '112 reference provides no suggestion for imaging the tissue with ^{23}Na or ^{39}K magnetic resonance to detect infracted myocardial tissue and provide contrast between the ventricular cavity and infarcted myocardial tissue, and thus evaluating the myocardial tissue. Moreover, the '112 reference states that "^{39}K MRI does not appear to be clinically feasible even with the use of optimized imaging parameters (col 11, lines 14 – 16). Further, as acknowledged by the Examiner, the '112 reference does not teach the use of an iron oxide contrast agent. In fact, the '112 reference does not teach the use of any contrast agent to attenuate the ^{23}Na or ^{39}K signal for ventricular blood and viable well-perfused tissue.

The teachings of the '121 reference do nor cure the flaws of the '112 reference. The Examiner alleges that the '121 reference "teaches a method of improving the contrast in MRI images by using a ferromagnetic or paramagnetic contrast agent such as an iron oxide bound to a polysaccharide to decrease the signal level of the targeted tissue relative to its surroundings

(Office Action, p.4)." The '121 reference teaches methods of generating enhanced images of the human or non-human animal body which involves administering to the body a positive MRI contrast agent following the particular mode of administration and negative MRI contrast agent, both of which are body tissue or body duct-specific (see, e.g. abstract). The '121 reference teaches that "for ferromagnetic and superparamagnetic contrast agents, which are negative MRI contrast agents, the enhanced image contrast derives primarily from the reduction in the spin reequilibration coefficient known as T2 or as the spin-spin relaxation time, a reduction arising from the effect on the imaging nuclei of the fields generated by the ferromagnetic or superparamagnetic particles (col 1, lines 31 – 37)." The '121 reference teaches that ferromagnetic and superparamagnetic MRI contrast agents can include iron oxide particles, either free or enclosed within or bound to a particle of a non-magnetic matrix material such as a polysaccharide (col 2, lines 26 – 30). The '121 reference provides methods for using ferromagnetic and superparamagnetic MRI contrast agents in methods of MRI imaging of tissues or organs. The '121 reference teaches exemplary use of the contrast agents for viewing anatomical structure:

> Thus the combination of positive and negative tissue specific MRI contrast agents allowed in vivo imaging of the anatomical structure of the liver to an extent that was not possible using either of the agents separately.

The '121 reference provides neither teaching nor suggestion of administering the contrast agents, in particular the iron oxide contrast agents, in the heart. As set forth in the specification and described above, imaging the heart presents unique problems of low spatial resolution which hinders differentiation between ventricular cavity and infarcted tissue. The '121 reference provides neither teaching nor suggestion for using the contrast agents in a method to provide contrast between ventricular cavity and infarcted myocardial tissue, and thereby provide an evaluation of myocardial tissue

The Examiner argues that "it would have been obvious to a person having ordinary skill in the art to modify the '112 reference to include the use of iron oxide to attenuate the ^{23}Na or ^{39}K MRI signal for ventricular cavity blood and viable well-perfused tissue (Office Action, p.4)."

The Examiner further argues that "(s)uch a modification would enable an enhanced image contrast so as to better distinguish viable and non-viable cardiac tissue, a criticality already established by the '112 reference (Office Action, p.4)." The instant specification not only teaches that imaging the heart presents unique problems of low spatial resolution which hinders differentiation between ventricular cavity and infarcted tissue, but further teaches use of an iron oxide agent to optimize ^{23}Na or ^{39}K MRI signals. For example, the specification teaches optimization of the iron oxide agent (MION-46) to provide contrast between the ventricular cavity and infarcted myocardial tissue:

> Referring now to FIG. 3, when the MION-46 dose (i.e. target dose) and TE are optimized for minimize signal intensity differences between ventricular cavity blood and well-perfused viable myocardium; maximize signal intensity differences between non-viable myocardium and ventricular cavity blood in myocardial infarction; and maximize signal intensity differences between non-viable myocardium and well-perfused viable myocardium in myocardial infarction, there is a hypointense signal in both ventricular cavities 33, 34 and ventricular wall 36 and a hypointense signal for the non-viable infarcted myocardium 38. Consequently, the major 23Na MRI signals correspond to the non-viable infarcted myocardium 38 (page 9, lines 18 – 26).

The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *Berghauser v. Dann, Comr. Pats.*, 204 U.S.P.Q. 393 (Dist. DC 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious. *Ex parte Hiyamizu*, 10 U.S.P.Q.2d 1393 (Bd. Pat. App. & Inter. 1988).

In the instant case, there is not sufficient motivation for one of skill in the art to modify the teachings of the '112 reference to include the use of an iron oxide agent as taught by the '121 reference. The '112 reference does not provide teaching beyond the manipulation and optimization of imaging parameters so as to increase the overall MR signals for ^{23}Na and ^{39}K to a

detectable level. The '121 reference generally teaches a method of improving the contrast in MRI images, but neither teaches nor suggests use of an iron contrast agent in the heart, and specifically a use for treating the myocardial tissue with an iron oxide contrast agent so as to attenuate the ^{23}Na or ^{39}K MRI signal to differentiate between ventricular cavity blood and viable well-perfused tissue.

Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Claims 8, 10 – 11, 23, 25, and 27 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Judd et al (the '112 reference) in view of Berg et al (the '121 reference), further in view of Weissleder (U.S. Patent No. 5,492,814; the '814 reference). Applicants respectfully traverse the rejection.

Claim 8 is dependent from claim 1, and teaches that the contrast agent comprises one or more iron atoms coordinated with a polymer having oxygen substitution.

The Examiner argues that "the '112 reference and the '121 reference disclose all of the limitations as discussed above (but) do not expressly disclose the use of an iron contrast agent with one or more iron atoms coordinated with a polymer having oxygen substitution, and with a dextran (Office Action, p. 4)." The Examiner argues that the '814 reference "teaches an iron oxide contrast agent for use in MRI, where the tissue imaged may be damaged heart tissue, such as infarcted myocardium, where the contrast agent has one or more iron atoms coordinated with a polymer having oxygen substitution (Office Action, p.5)."

As set forth above, the combination of the '112 reference and the '121 reference do not render the rejected claims unpatentable. Further, the '814 reference teaches methods for collecting data from biological tissue using magnetically active compounds, such as paramagnetic compounds, for magnetic resonance imaging (MRI). The '814 reference does not at all relate to a method or composition for performing ^{23}Na and ^{39}K MRI on cardiac tissues so as to address the problem of minimal signal intensity differences between the signal for infarcted cardiac tissue and ventricular blood present in the ventricular cavities. The '814 reference does not teach or suggest a method for evaluating myocardial tissue using ^{23}Na or ^{39}K MRI wherein the myocardial tissue is treated with an iron oxide contrast agent so as to selectively attenuate the

^{23}Na or ^{39}K signal for ventricular cavity blood and well-viable perfused tissue, as recited in Applicants' claim 1.

Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

CONCLUSION

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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